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Journal Name

ARTICLE

A facile one-pot method to synthesis of 2-alkylated indole and 2,2'-bis(indolyl)methane derivatives using ketones as electrophile and its anion sensing ability

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Indole derivatives are of great importance because of their biological activity and application in technology. This study explores the synthesis of 2-alkylated indoles derivatives and 2,2′-bis(indolyl)methanes, and their application in anion sensing. The synthesis of a wide range of 2-alkylated indoles and some 2,2′-bis(indolyl)methanes, which cannot be synthesized by previous reported methods, was first time accomplished employing a dipole exchange of the indole ring towards electrophilic substitution. Some of the indole derivatives exhibited selective recognition and sensing ability towards F^- and HSO_4^- anions through a naked-eye detectable color changes. The sensing details of the indole derivatives were also evaluated using UV-Vis spectroscopy and ^1H NMR titration techniques.

Introduction

Indole and its derivatives are frequently present in the structure of pharmaceutics, agricultural chemicals, functional substances and natural products.[1-3] Therefore, many studies have reported the effective derivatization of indole, and the development of new synthetic methods and application of new indole derivatives have been explored extensively since indole was discovered in 1869.[4-6] Bis(indolyl)methane alkaloids and substituted indole derivatives were previously discovered, and because of their importance in biology and technology applications, there has been an increasing interest to develop cheap, effective, and facile methods for synthesis of new derivatives.[7-12] But, the directly synthesis of 2-substituted indoles from indole are extremely difficult and limited. Consequently, the most frequently used methods to access 2-substituted indoles are often based on the construction of the heterocycles via cyclization reactions (Scheme 1a).[13,14] Despite its importance and widespread use, asymmetric bis(3-indolyl) methanes and symmetric/asymmetric bis(2-indolyl)methanes remain difficult to synthesize effectively, except for synthesis of symmetric bis(3-indolyl)methanes. In the literature, the studies concerning the synthesis of bis(2-indolyl)methanes are very restricted and these indoles are currently substituted at the 3-position (Scheme 1b).[15]

In our previous studies, we developed an efficient protocol for the preparation of 2-substituted indoles through Michael-type addition of 4,7-dihydroindole (**1**) using Michael acceptors as electrophile followed by an oxidation step (Scheme 1c).[16,17] Our strategy also provided the most important alternative option for accessing chiral 2-substituted indoles.[18] Herein, we aim to develop a highly efficient, facile and atom economical protocol to prepare 2-alkylated indoles and bis(2-indolyl)methanes (Scheme 1d). The synthesis of 2-alkylindoles are previsualized from Friedel-Crafts reaction between 4,7-dihydroindol (**1**) and ketones such as cyclic/acyclic aliphatic ketones, bisaryl ketones and aryl-alkyl ketones via redox isomerization including the dehydration and hydrogen shift as in situ. The preparation of bis(2-indolyl)methanes is predicted via two consecutive Friedel-Crafts alkylation of two equivalent of 4,7-dihydroindole (**1**) with one equivalent of a ketone followed by an oxidation step.

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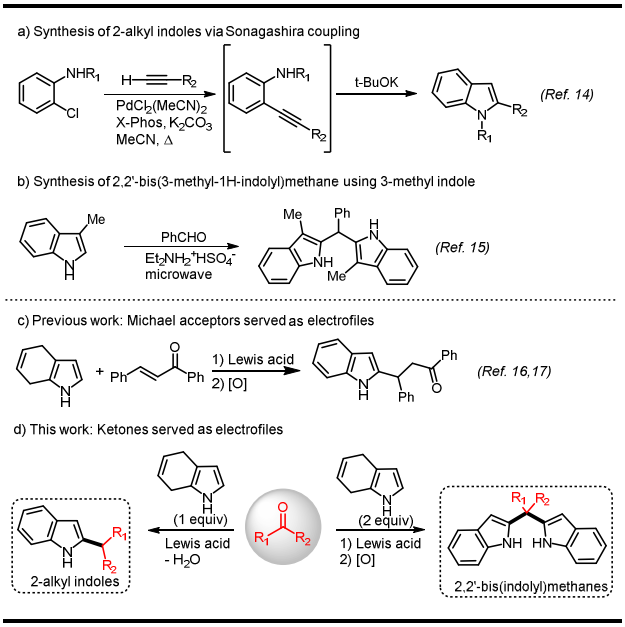


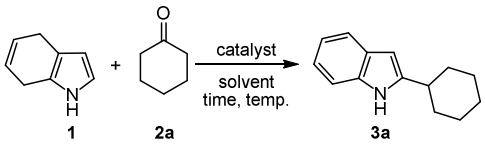
Scheme 1. Strategies for the synthesis of 2-alkyl indoles and 2,2'-bis(indolyl)methanes

Molecules such as indole, carbazole, bisindole and indolocarbazole form an import class of hydrogen bond donors. In addition to their biological properties, bis(indolyl)methane and alkyl indoles are very attractive compounds for chemosensing.[19-25] Because of their sensitivity and selectivity, these compounds have served in the determination of ions hazardous to the environment and health. Within this context, there is just an increasing interest in the synthesis of colorimetric sensors for detection of anions. Anions play an important role in chemical and biological systems, and fluoride, acetate and bisulphate anions sometimes play a role in environmental systems. For example, fluoride ion has an important application in the food and toxicity industry. Among the various anions, bisulphate ion is of particular interest because of its essential role in biological and industrial areas. Upon decomposition of bisulphate ion at high pH, toxic sulfate ion (SO_4^{2-}) is released, which can cause respiratory paralysis.[11] For these reasons, we are concerned with determining whether new indole derivatives have specific chemoselectivity for ions by using spectroscopic analysis methods, including UV-vis and NMR titration as well as the color change observed by the naked eye.

Results and discussions

At first, 4,7-dihydro-1*H*-indole (**1**) as staring material was obtained by Birch reduction of indole (**12**) with Li in liquid ammonia.[16] Our effort was initially focused on the alkylation of 4,7-dihydro-1*H*-indole (**1**) with cyclohexanone (**2a**) as a model reaction. As shown in Table 1, after treatment of **1** (1.0 equiv) with **2a** (1.0 equiv) in the presence of $Bi(NO_3)_3{\cdot}5H_2O$ (10% mol) in methylene chloride at room temperature, the desired alkylation product was not observed (Table 1, Entry 10). When the reaction was carried out using TFA (trifluoroacetic acid), $AlCl_3$ and PhCOOH as catalysts at room temperature, a complex product mixture was obtained. Therefore, optimization study was performed by varying the parameters such as reaction time, catalyst, temperature and solvent (Table 1). Notably, when the reaction was carried out at 80 °C in acetonitrile in the presence of the $Bi(NO_3)_3{\cdot}5H_2O$, the desired 2-alkylated indole **3a** was isolated in 97% yield (Table 1, Entry 11).

Table 1. Optimization of reaction conditions[a]

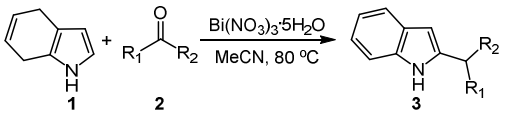


Entry	Catalyst	Solvent	Temp. (°C)	Time	Yield[b] (%)
1	TFA	CH_2Cl_2	25	30 min.	0[c,d]
2	$AlCl_3$	CH_2Cl_2	25	30 min.	5[c,d]
3	$ZrCl_4$	CH_2Cl_2	25	5h	25
4	$ZrCl_4$	MeCN	80	30 min.	15[c,d]
5	PhCOOH	MeCN	80	30 min.	17[c,d]
6	$Cu(OTf)_2$	MeCN	80	5h	80
7	$InCl_3$	MeCN	80	5h	75
8	$BiCl_3$	MeCN	80	5h	78
9	$Zn(OTf)_2$	MeCN	80	5h	88
10	$Bi(NO_3)_3{\cdot}5H_2O$	CH_2Cl_2	25	12h	0
11	$Bi(NO_3)_3{\cdot}5H_2O$	MeCN	80	5h	97

[a]**Conditions:** 4,7-dihydro-1*H*-indole (**1**, 1 equiv), cyclohexanone (**2a**, 1 equiv), catalyst (10% mmol) and solvent (10 mL). [b]Isolalated yields of 2-cyclohexyl-1*H*-indole (**3a**). [c]Complex reaction mixture. [d]Under N_2

With the optimized reaction conditions in hand, we next explored the scope and limitations of the reaction by using **1** (1.0 equiv) and various ketones (1.0 equiv) and the desired products (**3a-l**, **3o-p**) were obtained in high yields (Table 2). In contrast, the reaction of 2-acetylpyrrole (**2m**) failed to produce the desired product **3m** under the optimized conditions and only lead to the recovery of the starting material (Table 2). We assume that the possible resonance contribution for **2m** could decrease the reactivity of carbonyl carbon toward the nucleophilic attack of dihydroindole **1**. When *N*-Boc-2-acetylpyrrole (**2n**) reacted with **1**, the formation of a trace amount product **3n** was estimated by ^{1}H NMR spectra (Table 2).

Table 2. Substrate scope by varying ketones (1 equiv) with **1** (1 equiv)



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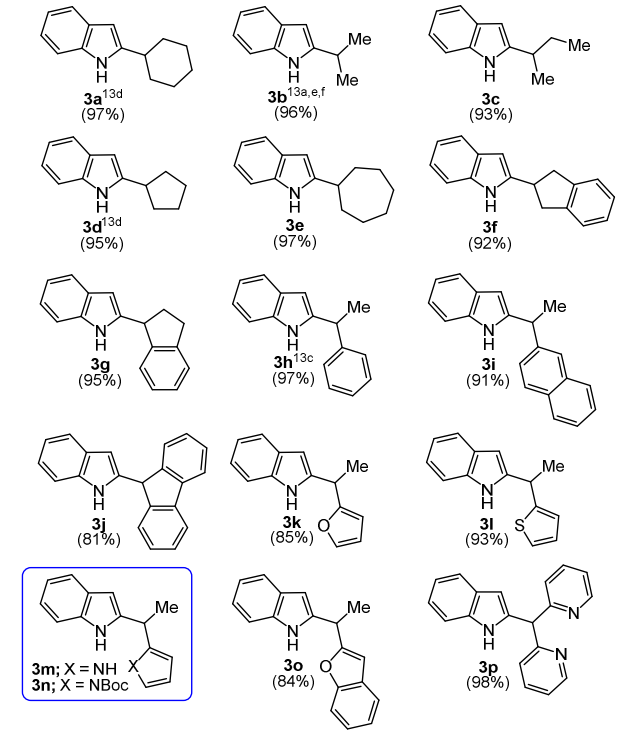
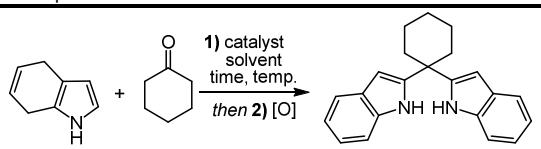


[a]**Conditions:** **1** (1.0 mmol), **2** (1.0 mmol), $Bi(NO_3)_3{\cdot}5H_2O$ (10% mmol), MeCN (10 mL), 80 °C, under air; isolated yields are shown.

We next examined the reaction between **1** (2.0 equiv) and ketones (1.0 equiv) to yield bis(2-indolyl)methanes. The reaction of **1** (2.0 equiv) and **2a** (1.0 equiv) was selected as model reaction, and carried out by changing the parameters such as reaction time, catalyst, temperature and solvent. Although the formation of the expected 2,2'-(cyclohexane-1,1-diyl)bis(4,7-dihydro-1*H*-indole) was confirmed by ^{1}H NMR spectra, the purification of the crude product by column chromatography on the silica gel failed. Therefore, we attempted to oxidize the crude product and to isolate the corresponding bis(2-indolyl)methane. Among the tested parameters as shown results in Table 3, the best result was obtained in refluxing acetonitrile with the catalyst of bismuth nitrate for 5 h to give **4a** in a yield of 74% followed by the usual work-up and the oxidation of the crude product with *p*-benzoquinone (PBQ) in methylene chloride (Entry 10).

Table 3. Optimization of reaction conditions[a]

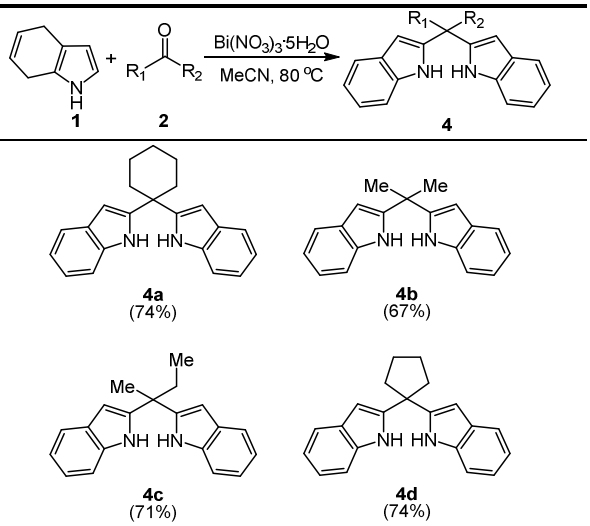


Entry	Catalyst	Solvent	Temp. (°C)	Time	Yield[b] (%)
1	TFA	CH_2Cl_2	25	30 min.	0[c]
2	$AlCl_3$	CH_2Cl_2	25	30 min.	10[c,d]
3	$ZrCl_4$	CH_2Cl_2	25	5h	12[d]
4	$ZrCl_4$	CH_3CN	80	30 min.	34[c,d]
5	PhCOOH	MeCN	80	30 min.	27[c,d]
6	$Cu(OTf)_2$	MeCN	80	5h	25
7	$InCl_3$	MeCN	80	5h	55
8	$BiCl_3$	MeCN	80	5h	71
9	$Zn(OTf)_2$	MeCN	80	5h	70
10	$Bi(NO_3)_3{\cdot}5H_2O$	MeCN	80	5h	74

[a]**Conditions: 1)** 4,7-dihydro-1*H*-indole (**1**, 2 equiv), cyclohexanone (**2a**, 1 equiv), catalyst (10% mmol) and solvent (10 mL) and then **2)** PBQ (*p*-benzoquinone, 2.5 equiv) and CH_2Cl_2 (25 mL). [b]Isolalated yields of 2,2'-(cyclohexane-1,1-diyl)bis(1*H*-indole) (**4a**). [c]Complex reaction mixture. [d]2-Cyclohexyl indole (**3a**) occurred.

Furthermore, although the reactions were performed over a wide range of ketones, the desired 2,2'-(bis-1*H*-indolyl)methanes **4a-d** were only able to be obtained from with cyclic or acyclic aliphatic ketones **2a-d** (Table 4, entry 1-4). In the case of the other ketones **2e-o**, while the reactions only gave the 2-alkylated indole derivatives **3e-o**, the excess of dihydroindole **1** was recovered (Table 4, entry 5-10). Similar results were likewise obtained from with excess equivalents, regardless of solvent and temperature conditions.

Table 4. Substrate scope by varying ketones (1 equiv) with 1 (2 equiv)



[a]**Conditions: 1)** **1** (2.0 mmol), **2** (1.0 mmol), $Bi(NO_3)_3{\cdot}5H_2O$ (10% mmol), MeCN (10 mL), 80 °C, under air; **2**) PBQ (2.5 equiv) and CH_2Cl_2 (25 mL), isolated yields are shown. Ketones **2e-o** provided 2-alkylated indoles.

A possible mechanism for the formation of the 2-alkylated indole **2a** and bisindolylmethane **4a** was formulated in Scheme 2. The formation of the 2-alkylated indole **2a** may proceed via an intermolecular Friedel-Crafts product **5** between pyrrole **1** and electrophile **2a** in the presence of the catalyst followed by a redox isomerization involving hydration and proton shift steps. In the presence of a Lewis acid, the intermediate **5** may be captured by a second equivalent of **1** as a nucleophile to afford bis-pyrrolyl-methane **7**, which readily oxidised to **4a** with PBQ. As mentioned above, the aryl-aryl or aryl-alkyl ketones under same conditions do not yield the expected bisindolylmethane derivatives in each case, but rather give the corresponding 2-alkylated indoles. We assume that the carbocation intermediate formed in the first step of the Friedel-Crafts reaction has a key role, in that it directly influences the progress of the reaction. Some representatives of the carbocation intermediates can be seen in Figure 1. We predict that the intermediate **6a** possess a coplanar structure, which can tolerate both reaction pathway. In case of the intermediate **6h** or **6p**, we propose that these carbocations are to be propeller-shaped due to steric crowding of the ortho hydrogens. Thus, these intermediates are twisted out of coplanarity, and their resonance stabilisation is decreased. With this closed geometry as a result of

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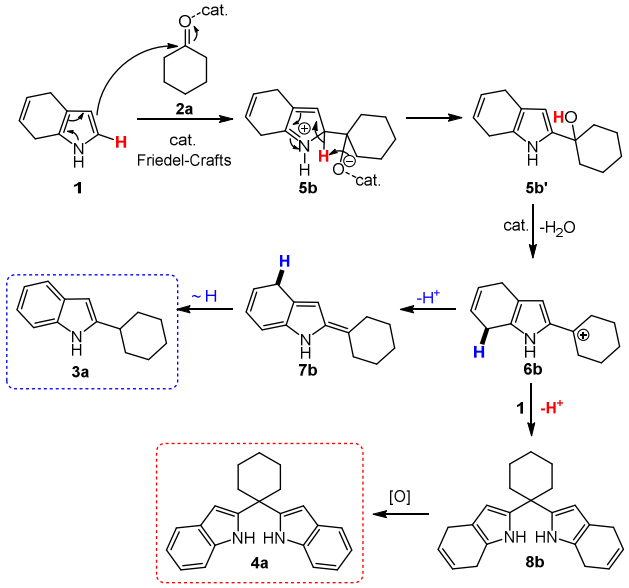
the steric hindrance, the empty p orbital of these carbocations is shielded from the approaching the second dihydroindole **1**, and the aromatization to second Friedel-Crafts reaction is preferred.



Scheme 2. Proposed mechanism for the formation of **3a** and **4a**

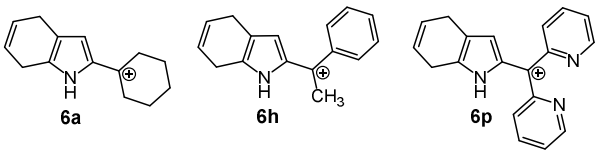
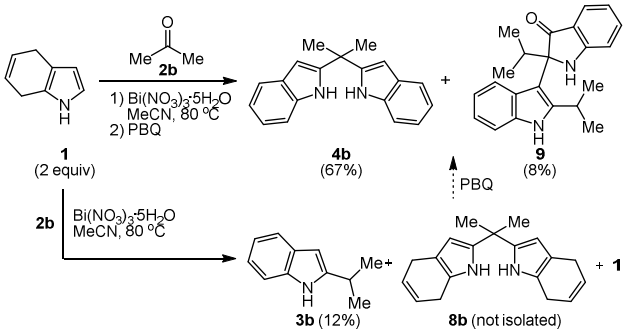
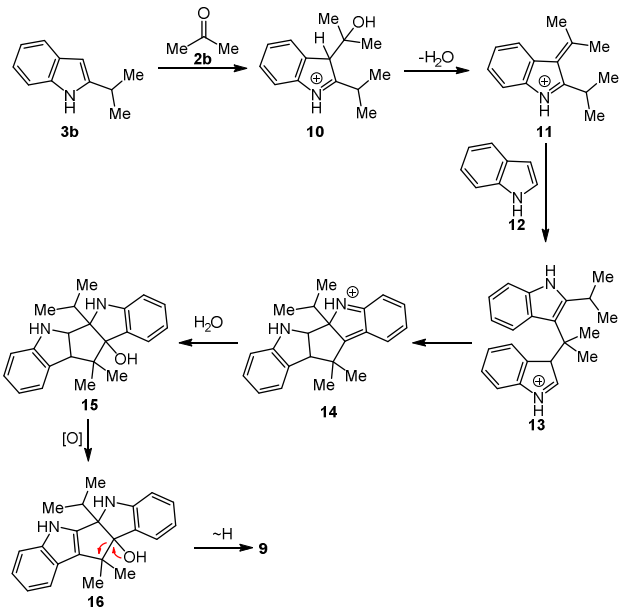


Figure 1. Representative carbocation intermediates

In order to synthesize 2,2'-(propane-2,2-diyl)bis(1*H*-indole) (**4b**), the reaction of 4,7-dihydro-1*H*-indole (**1**) with acetone (**2b**) was carried out (Scheme 3). The ^{1}H NMR spectrum of the crude reaction mixture shows a mixture of 2,2'-(propane-2,2-diyl)bis(4,7-dihydro-1*H*-indole) (**8a**) as main product and 2-alkylated indole **3b** as the byproduct along with unreacted **1**. During the separation over silica gel column, while **3b** isolated in 12% yield, the main product **8a** could not be obtained. Then, the crude mixture was submitted to the oxidation with *p*-benzoquinone in acetonitrile. After the purification, 2-isopropyl-2-(2-isopropyl-1*H*-indol-3-yl)indolin-3-one (**9**) as a novel indole derivative was isolated, as well as the targeted bisindolylmethane **4b**. The structure of **9** was established by NMR spectroscopy. The ^{1}H NMR spectrum of the indole derivative **9** showed signals at 7.95 and 5.08 ppm for the NH groups of indole and oxindole rings. The resonance signals for eight aromatic protons were observed at 6.77-8.02 ppm. Additionally, the resonances of the two isopropyl methine protons were present as a multiplet at 3.97-3.93 ppm and 3.15-3.12 ppm. Because of both the chirality resulting from possible blocked rotation of the bond between the indole and oxindole rings by two isopropyl groups and the quaternary stereogenic carbon center in oxindole ring, the methyl protons were resonated as four doublets at 1.32, 1.22, 0.95 and 0.88 ppm. The carbon resonance signal observed at 203.4 ppm on APT ^{13}C NMR of indole-oxindole derivative **9** confirms the existence of a ketone group in the molecule and the fourteen carbon resonance signals at the olefinic area support the proposed structure. Furthermore, the aliphatic quaternary carbon and methine carbon signals in **9** were observed at 75.0, 34.7 and 26.7 ppm, respectively, whereas the methyl carbons were resonated as four signals at 23.7-16.4 ppm due to chirality.



Scheme 3. Reaction of acetone (**2b**, 1 equiv) with **1** (2 equiv)



Scheme 4. Proposed mechanism for the formation of 2-isopropyl-2-(2-isopropyl-1*H*-indol-3-yl)indolin-3-one (**9**)

The probable mechanism for the formation of the unexpected product **9** is shown in Scheme 4. We believe that this product occurred through a series of reactions between 2-isopropyl-1*H*-indole (**3b**), acetone (**2b**) and indole (**12**). The mechanism involves bismuth nitrate-catalyzed nucleophilic addition of 2-alkylated indole **3b** to acetone to afford the intermediate **10**. The subsequent dehydration of **10** is likely to proceed via the formation of an azafulvenium salt which in turn undergoes further addition with indole (**12**) derived from the oxidation of dihydroindole **1** by PBQ as in situ leading to the formation of iminium intermediate **13**. The proposed mechanism completes a subsequent intramolecular nucleophilic addition of **13** followed by the hydration, oxidation and oxidative C-C bond cleavage steps to afford **9**.

In connection with studies on the synthesis of bisindolylmethanes, the reaction of 4,7-dihydro-1*H*-indole (**1**; 2.0 equiv) and 2-acetylfuran (**2k**; 1.0 equiv) gave a mixture resulting in the formation of two unexpected products **17** and **12** along with 2-alkylated indole **3k** without the oxidation reaction (Scheme 5). This surprising result may be due to a hydride transfer from **1** to the

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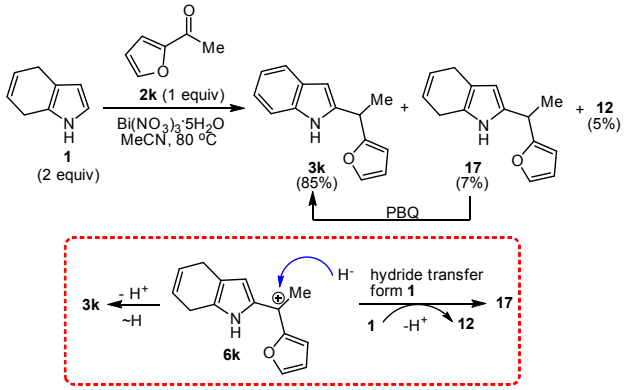
initially formed intermediate **6k** to yield **17** and **12** via an intermolecular redox-type reaction (Scheme 5).



Scheme 5. Reaction of **1** (2 equiv) with **2k** (1 equiv) and proposed mechanism for the products

Next, the sensing abilities of some of appropriate H-donor receptors depicted in Figure 2 were monitored by UV–vis, ^{1}H NMR spectroscopic methods and naked-eye observation. As an initial test, we checked the colour changes of receptors in various solvent systems (MeCN, MeCN/H_2O, DMSO, THF, THF/H_2O etc.) upon the addition of tetrabutylammonium (TBA) salts of F^-, Cl^-, Br^-, I^-, HSO_4^-, AcO^-, CN^- and SCN^-. As shown in Figure 2, a noticeable color changes by the naked eye could be detected from the interaction of **3l** with F^-, **4b** and **4c** with HSO_4^-. The interactions between other anions and receptors did not result in selective color changes.

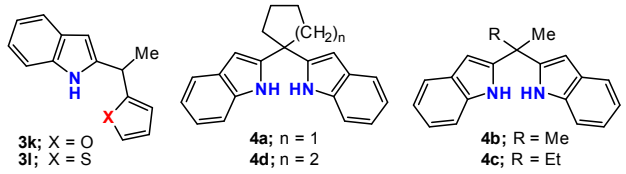


Figure 2. Structures of the receptors

Anion recognition properties of receptors with the aforementioned anions in the various solvent systems were further evaluated by UV-vis absorption spectroscopy (Figure 4). The free receptor **3l** displayed two sharp absorption peaks at 226 nm and 273 nm. Interaction of **3l** (1×10^{-5} M) with anions caused changes to appear in this region of the spectrum. Upon addition of F^-, the sharp peaks at 226/273 nm red shifted to 270/320 nm, which was attributed to the color change resulting from the interaction of **3l** with F^- ions that can be detected by the naked eye. Furthermore, a new absorption peak formed at 573 nm (Figure 4a). The UV-vis spectrum of **4a** in CH_3CN/H_2O (4:1, v/v) showed two sharp peaks at 250 and 290 nm. Upon addition of SCN^-, F^-, HSO_4^-, and CN^-, a new peaks for **4a** were observed at 515, 525, 530, and 540 nm, respectively (Figure 4b). Although a red-shift occurred as a result of interaction of **4a** with anions, **4a** was not selective. Different solvents and pH systems were explored, but in each case, there was no selectivity for a specific anion. It was determined that the two sharp characteristic peaks of **4b** shifted from 246/293 nm to 248/294 nm (shift to red) resulted from the interaction of **4b** with HSO_4^- ion, and a new interaction absorption peak formed at 520 nm (Figure 4c). It was noted that **4c** showed similar behaviors in CH_3CN/H_2O (4:1, v/v), and the interaction with HSO_4^- led to a decrease in sharp bands at 245/289 nm and a shift to 237/272 nm (blue-shift). A further peak formed at 505 nm due to the interaction (Figure 4d). A series of control studies with the naked eye and UV-vis showed that there was no color change observed for anions in solutions containing only MeCN.

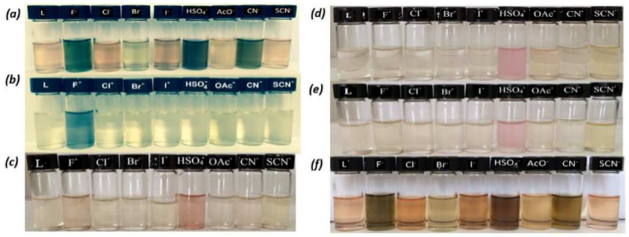


Figure 3. Clour changes obresved upon addition of 5×10^{-5} M anions to MeCN (**a**, **b**) or MeCN/H_2O (4:1, v/v) (**c**-**f**) of 1×10^{-5} M ligands [**3k** (a), **3l** (b), **4a** (c), **b** (d), **4c** (e) and **4d** (f)]

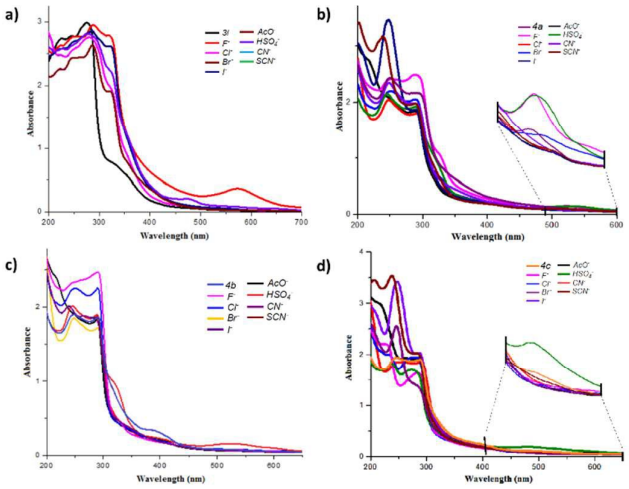


Figure 4. Change in the UV-vis absorption spectrum of ligands [**3l** (a), **4a** (b), **4b** (c) and **4c** (d); (1×10^{-5} M)] in MeCN (**a**) or MeCN/H_2O (4:1, v/v) (**b**-**d**) solution upon additions of anions (F^-, Cl^-, Br^-, I^-, HSO_4^-, AcO^-, CN^- ve SCN^-; tetrabutyl ammonium salts, 5×10^{-5} M)

Following these results, UV-vis and ^{1}H NMR spectrophotometric titrations were conducted in order to understand the binding phenomena of receptors with F^- and HSO_4^-. First, interaction of **3l** and F^- ions was carried out in a concentration of $[Bu_4N]F$ from 0 to 100 equivalents. It was observed that the sharp peaks at 226/273 nm of the receptor decreased upon interaction with 2 equivalent of F^-, and they shifted to 270/320 nm upon increasing $[Bu_4N]F$ concentration. Furthermore, a new band formed at 573 nm, and its intensity increased as the $[Bu_4N]F$ concentration increased. A new peak at 573 nm and a very radical color change were attributed to the exchange of N-H proton of indole unit, which was caused by the interaction with F^- (Figure 5a and 5b). The titrations of bis(2-indolyl)methanes **4b** (1×10^{-5} M) and **4c** (1×10^{-5} M) with HSO_4^- were realized with increasing concentration of $[Bu_4N]HSO_4$ from 0 to 100 equivalent. The intensity of the sharp peaks at 246/293 nm of **4b** increased upon the addition of 1 equivalent of $[Bu_4N]HSO_4$, and a new red-shifted peak was observed at 520 nm (Figure 6a and 6b). The interaction of **4c** with 1 equivalent of HSO_4^- anion resulted in a blue-shift and the formation of an additional new band at 505 nm (Figure 7a and 7b). It should be noted that fluorescence studies on the receptor-anion interactions did not show any fluorescence emission.

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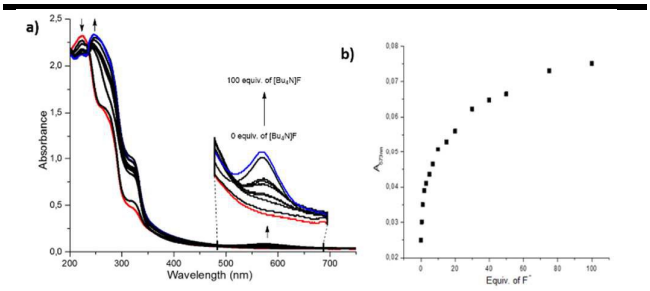

Figure 5. a) UV-vis titration of the sensor **3l** (1×10^{-5} M) in CH_3CN solution with standard solution of $[Bu_4N]F$, **b)** Absorption of sensor **3l** at 573 nm *vs.* equivalent of fluoride anion

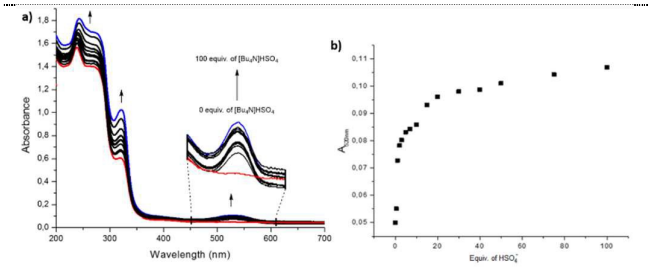

Figure 6. a) UV-vis titration of the sensor **4b** (1×10^{-5} M) in CH_3CN solution with standard solution of $[Bu_4N]HSO_4$, **b)** Absorption of sensor **4b** at 520 nm *vs.* equivalent of bisulfate anion

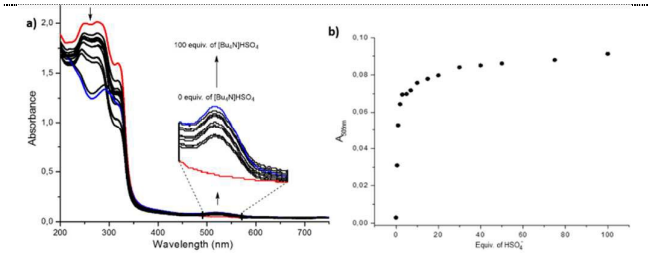

Figure 7. a) UV-vis titration of the sensor **4c** (1×10^{-5} M) in CH_3CN solution with standard solution of $[Bu_4N]HSO_4$, **b)** Absorption of sensor **4c** at 505 nm *vs.* equivalent of bisulfate anion

To obtain insight into the binding ability of the receptors with F^- and HSO_4^-, ^1H NMR titration experiments were carried out in CD_3CN at 298 K. It is clear that the broad signal of NH proton of the indole moiety disappeared when 2.0 equivalent of $[Bu_4N]F$ was added into a solution of **3l**. This indicates the formation of strong hydrogen bond between fluoride anion and active NH group (Figure S21, **ESI**). With increasing additional equivalents of F^-, the signals of H_a, H_b, H_d (indole) and H_f (thiophene) of **3l** showed upfield shifts, whereas the signal of He (indole) shifted toward downfield. To elucidate the binding mode of the bis(2-indolyl)methanes **4b** and **4c** with increasing HSO_4^- (from 0 to 10 equivalent), ^1H NMR titration spectra were undertaken, which illustrated the characteristic structural changes that occurred upon interaction with $[Bu_4N]HSO_4$ in CD_3CN at 298 K. While the signal of NH proton of indole of **4b** continuously shifted downfield, the signals of H_a, H_b, H_d protons exhibited upfield shifts, and the H_e proton shifted slightly downfield (Figure 8). With increasing equivalent of HSO_4^-, a downfield shift of the NH proton from 9.04 to 9.48 ppm of **4c** was especially observed (Figure S22, **ESI**). The evidence above can be ascribed to a hydrogen bonds are responsible for observed chemical shifts upon NH-floride ion and NH-bisulfate ion interactions (Figure 9). Thus, these interactions, which induce polarization of N-H bond, where the partial positive charge creates a downfield shift. Consequently, the increasing electron density on the indole ring promotes an upfield shift of the C-H protons and especially C3-H proton in pyrrole moiety.

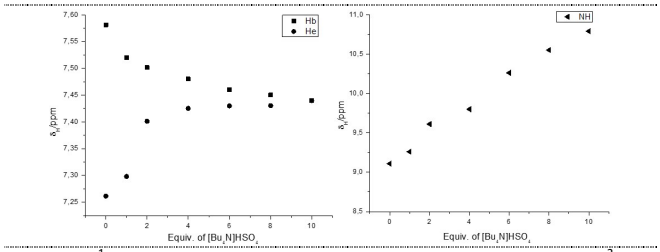

Figure 8. ^1H NMR (400 MHz) spectra in CD_3CN of the sensor **4b** (1×10^{-2} M) with presence of $[Bu_4N]HSO_4$; (**a**) 0 equiv. of $[Bu_4N]HSO_4$, (**b**) 1 equiv. of $[Bu_4N]HSO_4$, (**c**) 2 equiv. of $[Bu_4N]HSO_4$, (**d**) 4 equiv. of $[Bu_4N]HSO_4$, (**e**) 6 equiv. of $[Bu_4N]HSO_4$, (**f**) 8 equiv. of $[Bu_4N]HSO_4$ and (**g**) 10 equiv. of $[Bu_4N]HSO_4$

Conclusions

In conclusion, the synthesis studies to create 2-alkylated indoles and bis(2-indolyl)methanes are very limited. Therefore, we have designed and reported an effective and inexpensive method for the synthesis of new 2-alkylated indoles and bis(2-indolyl)methanes from 4,7-dihydroindole (**1**) using various ketones as the electrophile source of the alkylation and the formation mechanisms are also discussed. Furthermore, studies concerning the chemosensor properties of these 2-alkylated indoles and bis(2-indolyl)methanes were performed, and some of these derivatives show sensing of F^- and HSO_4^- anions via naked eye detection of color changes as well as of absorption signals. The interactions of the receptor and anions were further studied using ^1H NMR titrations. Reactions using aldehydes are currently underway.

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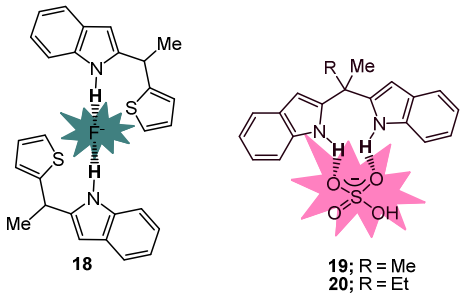

Figure 9. Plausible intermediates from the interaction between receptors with fluoride and bisulphate anions

Experimental section

General procedure (GP1) for the synthesis of 2-alkylated indoles: To a solution of 4,7-dihydro-1*H*-indole (**1**; 1.0 equiv) in MeCN (5 mL) was added ketone (**2a-p**; 1.0 equiv) and $Bi(NO_3)_3{\cdot}5H_2O$ (0.1 mmol). The reaction mixture was stirred magnetically in a flask at 80 °C. The reaction was monitored by TLC. After the completion of the reaction, the mixture was diluted with ethyl acetate (30 mL) and washed with water (2×50 mL). The organic phase was collected, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel column chromatograph and isolated compounds were given according to the elution sequence (EtOAc/Hexane) in general.

2-Cyclohexyl-1*H*-indole (3a): $Bi(NO_3)_3{\cdot}5H_2O$ (0.1 mmol)-catalyzed reaction of 4,7-dihydro-1*H*-indole (**1**; 200 mg, 1.68 mmol) with cyclohexanone (**2a**; 165 mg, 1.68 mmol) was performed at 80 °C for 5h in MeCN according to GP1. After purification, 2-cyclohexyl-1*H*-indole (**3a;** 325 mg (97%), yellow viscous liquid) was obtained. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.91 bs, NH, 1H), 7.53 (d, *J* = 7.7 Hz, =CH, 1H), 7.30 (d, *J* = 7.7 Hz, =CH, 1H), 7.13-7.04 (m, =CH, 2H), 6.23 (s, =CH, 1H), 2.75-2.69 (m, CH, 1H), 2.10-2.07 (m, CH_2, 2H), 1.87-1.74 (m, CH_2, 2H), 1.54-1.29 (m, CH_2, 6H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 145.3, 135.7, 128.8, 121.1, 120.1, 119.8, 110.5, 97.7, 37.5, 29.9, 26.5, 26.3; **IR (KBr, cm^{-1}):** 3335, 2921, 2871, 1624, 1452, 1431, 1397, 1356, 1163, 1122, 908, 858, 811; **Anal. Calcd.** for $C_{14}H_{17}N$: C, 84.37; H, 8.60; N, 7.03; found: C, 84.32; H, 8.10; N, 7.27; **TLC:** R_f = 0.72 (EtOAc/hexane (5%), 254 nm).

2-(1-(Thiophen-2-yl)ethyl)-1*H*-indole (3l): $Bi(NO_3)_3{\cdot}5H_2O$ (0.1 mmol)-catalyzed reaction of 4,7-dihydro-1*H*-indole (**1**; 200 mg, 1.68 mmol) with 1-(thiophen-2-yl)ethan-1-one (**2l**; 212 mg, 1.68 mmol) was performed at 80 °C for 5h in MeCN according to GP1. After purification, 2-(1-(thiophen-2-yl)ethyl)-1*H*-indole (**3l;** 355 mg (93%), a pale red solid, m.p. = 65-66 °C (CH_2Cl_2/hexane)) was obtained. **^{1}H NMR (400 MHz, $CDCl_3$):** δ): δ 7.82 (bs, NH, 1H), 7.57 (d, *J* = 7.7 Hz, =CH, 1H), 7.27-7.26 (m, =CH, 1H), 7.25 (d, *J* = 1.1 Hz, =CH, 1H), 7.15-7.06 (m, =CH, 2H), 6.98-6.96 (m, =CH, 1H), 6.91-6.90 (m, =CH, 1H), 6.41 (s, =CH, 1H), 4.59-4.54 (m, CH, 1H), 1.80 (d, *J* = 7.0 Hz, CH_3, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 148.4, 142.5, 136.2, 128.7, 127.0, 124.4, 124.3, 121.8, 120.5, 120.0, 110.8, 99.4, 34.8, 22.5; **IR (KBr, cm^{-1}):** 3082, 3028, 2972, 2839, 1605, 1479, 1452, 1384, 1332, 1309, 1256, 1232, 1184, 1023, 882, 824; **Anal. Calcd.** for $C_{14}H_{13}NS$: C, 73.97; H, 5.76; N, 6.16; S, 14.11, found: C, 73.88; H, 5.72; N, 6.24; S, 14.13; **TLC:** R_f = 0.52 (EtOAc/hexane (15%), 254 nm).

General procedure (GP2) for the synthesis of 2,2'-bis(indolyl)methanes: To a solution of 4,7-dihydro-1*H*-indole (**1**; 2.0 equiv) in MeCN (5 mL) was added ketone (**2a-p**; 1.0 equiv) and $Bi(NO_3)_3{\cdot}5H_2O$ (0.1 mmol). The reaction mixture was stirred magnetically in a flask at 80 °C. The reaction was monitored by TLC. After the completion of the reaction, the mixture was diluted with ethyl acetate (30 mL) and washed with water (2×50 mL). The organic phase was collected, dried over Na_2SO_4, filtered and concentrated. The crude product was dissolved in CH_2Cl_2 (15 mL) and *p*-benzoquinone (2.0 equiv.) was added. The mixture was stirred at the room temperature for overnight. After completion of the reaction, the solvent was evaporated and the crude product was dissolved with ethyl acetate (30 mL) and the organic phase was washed with NaOH (2N, 2×30 mL), brine (30 mL), and dried over Na_2SO_4. The crude product was purified by silica gel column chromatograph and isolated compounds were given according to elution sequence (EtOAc/Hexane) in general.

2,2'-(Cyclohexane-1,1-diyl)bis(1*H*-indole) (4a): $Bi(NO_3)_3{\cdot}5H_2O$ (0.1 mmol)-catalyzed reaction of 4,7-dihydro-1*H*-indole (**1**; 300 mg, 2.52 mmol) with cyclohexanone (**2a**; 124 mg, 1.26 mmol) was performed at 80 °C for 2h in MeCN. *p*-Benzoquinone (272 mg, 2.52 mmol) was added to the reaction mixture (405 mg) according to GP2. After purification, 2,2'-(cyclohexane-1,1-diyl)bis(1*H*-indole) (**4a;** 292 mg (74%), red solid, m.p. = 101-102 °C (CH_2Cl_2/hexane)) was obtained. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.74 (bs, NH, 2H), 7.59 (d, *J* = 7.9 Hz, =CH, 2H), 7.20 (d, *J* = 7.9 Hz, =CH, 2H), 7.13-7.07 (m, =CH, 4H), 6.55 (s, =CH, 2H), 2.34-2.31 (m, CH_2, 4H), 1.72-1.67 (m, CH_2, 4H), 1.57-1.55 (m, CH_2, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 144.1, 136.1, 128.5, 121.9, 120.4, 120.0, 111.0, 99.5, 41.0, 36.8, 26.2, 23.0; **IR (KBr, cm^{-1}):** 3039, 2968, 2928, 2109, 1509, 1464, 1451, 1305, 1228, 1163, 1122, 1084, 979, 908, 870, 811; **Anal. Calcd.** for $C_{22}H_{22}N_2$: C, 84.04; H, 7.05; N, 8.91, found: C, 84.06; H, 7.01; N, 8.87; **TLC:** R_f = 0.29 (EtOAc/hexane (15%), 254 nm).

Acknowledgements

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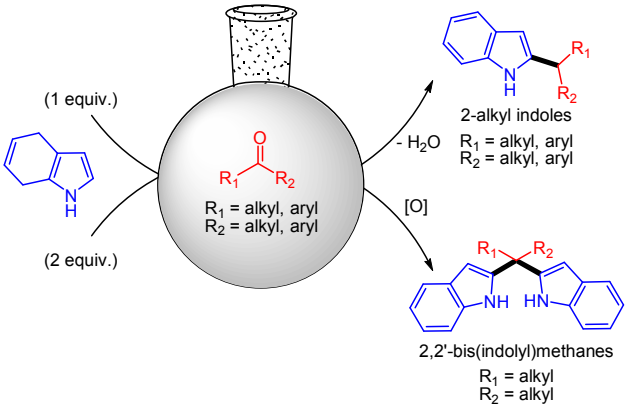

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